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ELECTRODES FOR FUNCTIONAL ELECTRICAL STIMULATION

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TABLE OF CONTENTS

SECTION A. CLINICAL COLLABORATION

Meetings were held with both our upper extremity and our lower extremity collaborators. The focus of these meetings was to review with our collaborators the workscope of this contract award, to discuss their continuing clinical problems with electrodes, and to begin development of a plan for human feasibility testing, as is outlined in Section E of this report.

A.2: Upper Extremity

Our upper extremity collaborators have significant experience in the development and implementation of their fully implantable neuroprosthetic hand grasp system. This system has been developed over the last several decades, and utilizes intramuscular and epimysial electrodes placed in multiple sites of the arm. The collaborators are generally pleased with the success of the system and its ability to provide adequate control for the indicated functional outputs, the 2 grasp patterns of lateral and palmar prehension.

A concern in all implantable systems is the volume of hardware placed in the body. With their current system, our collaborators are comfortable with the number of leads required. However, they foresee future systems that may include additional electrodes, placing them at or near the limit of tolerable numbers of implanted electrodes, leads, and connectors. Cuff electrodes could potentially reduce the volume of implanted hardware, but only if each cuff could control multiple muscles. However, the reduction in volume would have to be significant to be used as the basis for selecting cuff electrodes over muscle-based electrodes in a hand grasp system.

As with any surgical intervention, the number and size of incisions is ideally minimized. In their current upper extremity system, only 4 incisions are required to implant the electrodes. A substantial reduction in the necessary incisions would be attractive to the collaborators, but is probably unlikely with cuff electrodes. Unless a single cuff could control all the necessary muscles, multiple cuffs at multiple exposure sites would likely be required.

Muscle-based electrodes in the upper extremity system produce graded muscle contractions. The collaborators are happy with the degree of gradation available through these electrodes, and have concerns about the degree of muscle force gradation available through cuff electrodes. This concern will be addressed during this contract. Muscle-based electrodes in the upper extremity suffer from some length-dependent recruitment properties, which is one limitation the collaborators have to work with. Cuff electrodes should be less prone to length-dependent properties.

A.3: Lower Extremity

Our collaborators in the lower extremity have recently begun a series of implants using intramuscular and epimysial electrodes to effect standing for aid in patient transfers. A number of implants have already been performed, with electrodes placed in the vicinity of the gluteal nerve. The researchers have found that the depth of the implant site is an issue for them: the target nerve is several cm (5-10) below the skin, and the exposure provides limited working space. This is a particular problem because although the electrodes are not 'nerve' electrodes, they are in fact, often times sutured to the tissue immediately surrounding the gluteal nerve. The suturing requires additional work space than would be necessary for intramuscular or nerve cuff electrode implantation. Once the electrodes are implanted, our collaborators have continuing concerns about their stability and about the extent of muscle recruitment available through the electrodes.

Unlike the upper extremity research, lower extremity systems are still in beginning stages of development. This works to our advantage, in that the incorporation of cuff electrodes within these developing systems is likely to be more easily facilitated. While the upper extremity collaborators are faced with cuff electrodes being an alternative solution to issues that have previously been resolved, the lower extremity collaborators are still struggling with some of their system limitations, such as electrode stability and adequate muscle force generation, and cuff electrodes are potentially the solution.

The material described in the next section, B.2.1.2, on PMP electrodes, is considered confidential.

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SECTION B. DESIGN AND FABRICATION OF ELECTRODES, LEADS AND CONNECTORS

B.2.1.2: Polymer-Metal Foil-Polymer (PMP) Cuff Electrodes

We propose to develop a novel technique for cuff manufacture that would improve the mechanical reliability of the cuff, as well as incorporate automated methods of manufacture. In this new technique, the basic building block of the cuff will be platinum foil covered with a laser ablatable polymer, creating a polymer-metal-polymer (PMP) structure. Patterns left after cutting through the PMP structure with a laser will define the conductor pathways, the termination pads used to accommodate electrical connection to the leads, and the electrode pads that will act as conducting surfaces through which current is passed into the tissue medium.

A brief description of the fabrication steps we anticipate for the manufacture of the PMP electrode is provided here. We expect to first send to PI Medical a solid piece of platinum foil. PI Medical will laser machine a pattern of holes through the platinum foil, and return this piece to us. The pattern of holes is designed to improve the flexibility and provide sites for stress relief of the foil. Once we have received the patterned foil, we will sandwich the foil in silicone rubber, and send the laminated foil back to PI Medical for the second pass of laser machining. In the second pass, the laser will cut through both the elastomer and the foil, effectively isolating the four electrical paths. Additionally, the laser will be used to ablate the silicone rubber overlying the electrode contacts and the bonding pads, where lead wire will be connected to the substrate. Finally, the laser will be used to excise the final electrode piece, with dimensions approximating 25 x 4 mm. This piece will be returned to us to be incorporated in a spiral cuff.

Working with PI Medical, we have begun our efforts to implement this design. PI Medical will both supply the laser ablatable polymer and perform the laser machining of the metal foil and the PMP laminate. As such, we have been working with PI Medical in discussing issues involving both the machining and the silicone rubber material.

Foil Stability

For the extensive laser machining that is to be performed to create the entire pattern of holes, the foil must maintain its positional stability in all three dimensions. There is some concern that the amount of laser machining that is to be performed will cause heating of the platinum foil, and may result in some buckling, further stressing the need to keep the foil in a stationary position. A frame has been designed and machined that is intended to secure the foil along both its length and width during the machining process, and will further serve to ease in the handling of the rather delicate metal foil. The frame consists of two matching pieces of stainless steel that are secured at their corners with 4 screws. The foil is sandwiched between the two pieces of the frame, and secured by tightening the screws. The frame has an open interior, where the platinum foil is exposed and the machining will be performed. This simple frame design will be used in the initial attempts at PMP manufacture, but may require future modifications or re-design based on those initial experiences.

Machining Parameters

Samples of platinum foil, both 25 and 50μm thicknesses, have been sent to PI Medical for preliminary laser machining; they report that limited machining has been performed on both sample thicknesses. Edge definition is improved and laser time is reduced for the 25μm thick pieces than for those 50μm thick pieces, as could be expected. However, machining of both samples was considered successful by the laser machinist. A sample piece with multiple laser cuts has been returned and was examined using a scanning electron microscope.

The sample piece contained three different types of laser machined holes, as the processors were trying to determine the best method to cut the foil and to test the flatness of the foil within the frame. In the first method, the laser beam was moved around the perimeter of the desired hole multiple times until the center piece of foil dropped out. Examples of these cuts are presented in

Figures 1-3. In the alternate method of cutting, the laser beam was raster scanned across the desired hole shape. Examples of these cuts are presented in Figures 4-7. Finally, the processor laser machined holes using the same perimeter technique as in Figures 1-3, but performed this at multiple sites along the edge of the foil nearest the frame. This was intended to test the flatness of the foil as it was secured in the frame. Examples of these cuts are presented in Figures 8-9.

As is apparent in the figures, edge definition is improved for those holes machined using the perimeter cutting technique as compared to those holes machined using the raster scanning technique. In the PMP electrode design, the slots to be machined are 100μm in width, five times the largest burr on the raster scanned hole (20μm, Figure 6). Because of the difference in edge definition, the perimeter technique will be used in machining the PMP electrodes. A discoloration in the foil in the region immediately surrounding the holes can be noted, particularly in Figures 1, 2 and 8. This discoloration may be indicative of a heat affected zone in the platinum foil due to the laser machining, similar to what occurs in the regions surrounding welds. Further investigations of these discolored regions will be pursued in the following months. Particular consideration will be given to annealing the foil after the initial laser machining is performed.

The burrs shown in the figures appear to be generally rounded and to have a low profile. However, as the photos were taken facing the foil, we cannot be certain of the height of these burrs. Any significant height or sharpness of the burrs may lead to damage to the silicone rubber lamination that is applied around the foil. We will perform additional microscopic studies on these laser cuts and burrs and determine whether the burr profiles are of the size or shape that efforts should be made to further minimize them.

In the coming months, we will work with PI Medical to optimize the laser cutting parameters. Based on the photomicrographs, we can see that the laser parameters and method of cut have a significant effect on edge definition and burr size, and may also contribute to the discoloration of the foil that may be indicative of a heat affected zone. Increasing power on the laser beam may result in improved edge definition, but also may result in increased heating of the foil, with subsequent metallurgical changes and possible buckling. We will provide PI Medical with additional samples of platinum foil for laser machining with the specific intent of investigating changes in the laser parameters that will minimize burr size and thermal damage.

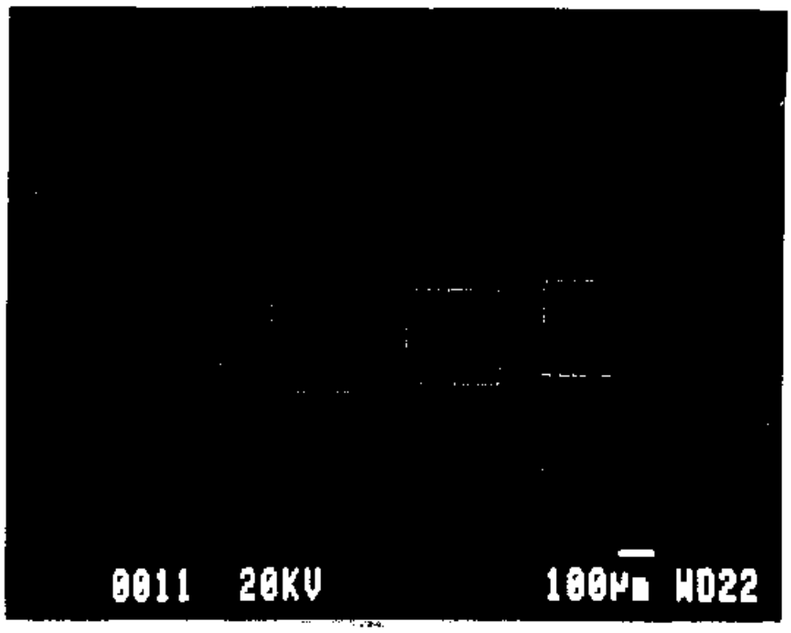


Figure 1: SEM photomicrograph of 4 holes laser machined through 25µm thick platinum foil, created by moving the laser beam around the perimeter of the desired hole multiple times. 50x

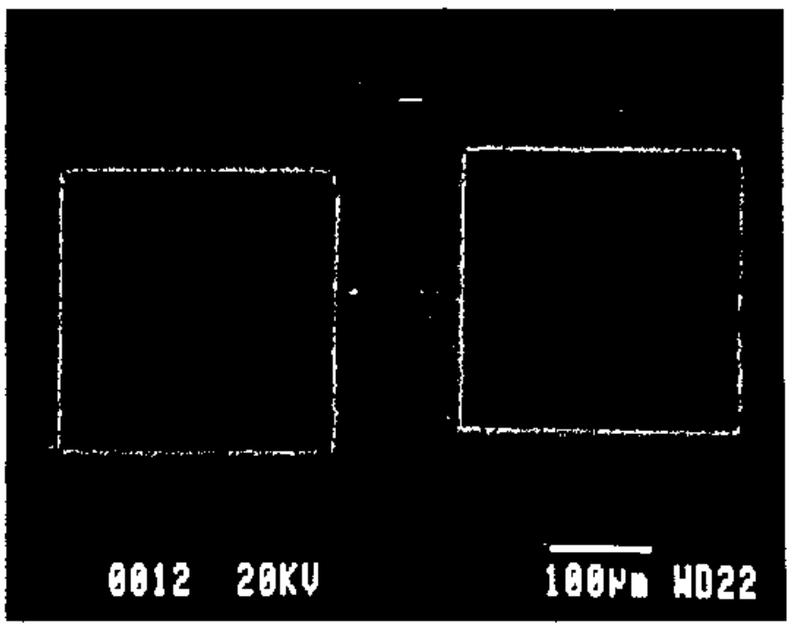


Figure 2: SEM photomicrograph of center 2 holes shown in Figure 1. A discoloration can be noted both in this figure and the figure above in the region of foil surrounding the machined hole. 150x

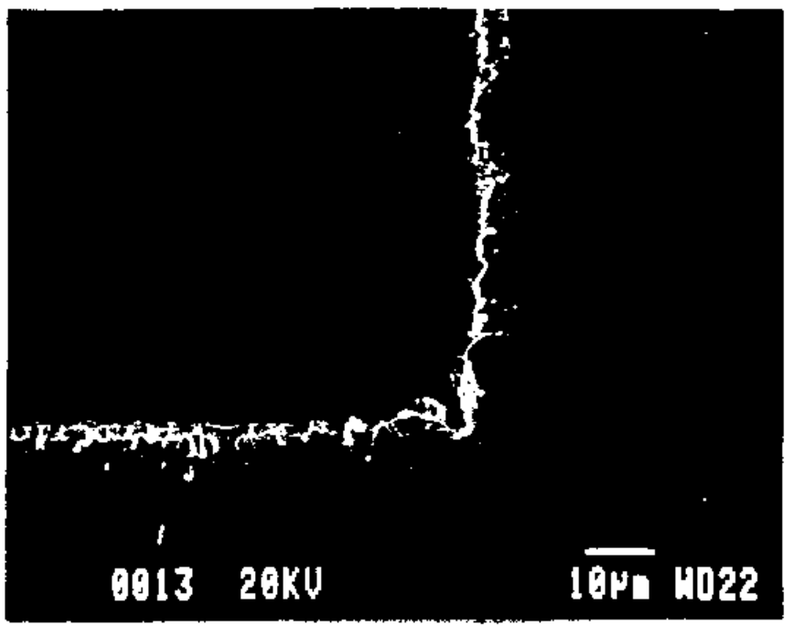


Figure 3: SEM photomicrograph at higher magnification of lower right corner of the left hole in Figure 2. Edge definition is good. 1000x

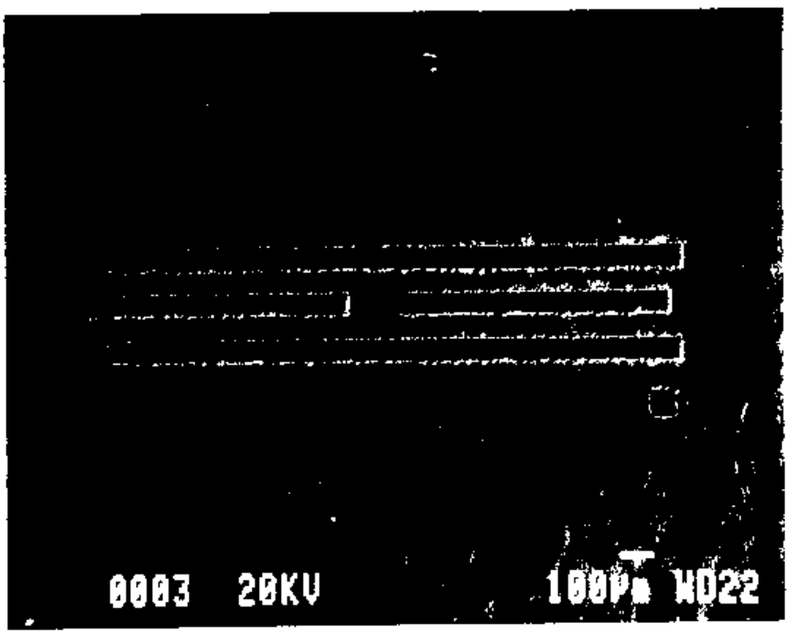


Figure 4: SEM photomicrograph of holes machined through 25µm thick platinum foil, created by raster scanning the laser beam over the desired hole. 50X

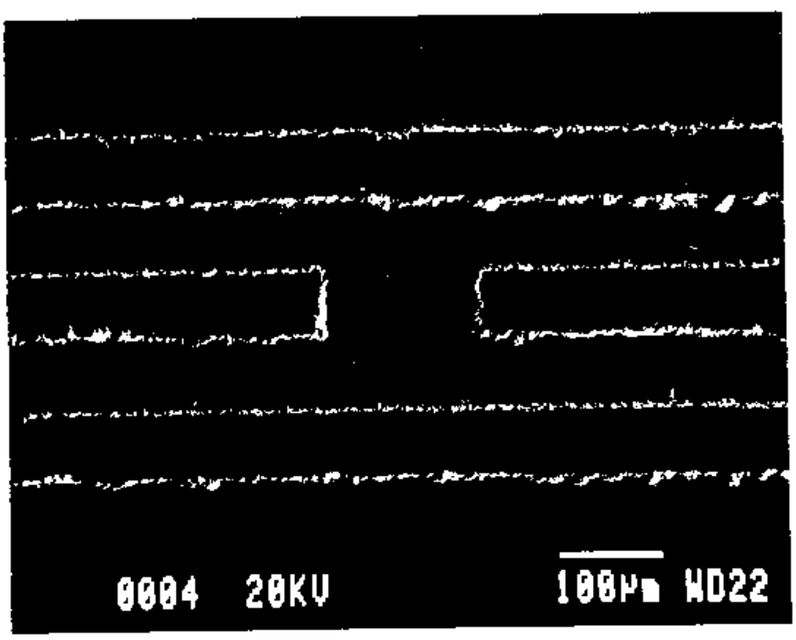


Figure 5: SEM photomicrograph at higher magnification of Figure 4. 150X

Figure 6: SEM photomicrograph at higher magnification of center left slot shown in Figure 5. Entry definition is reduced and burrs up to 20µm are seen. 1000x

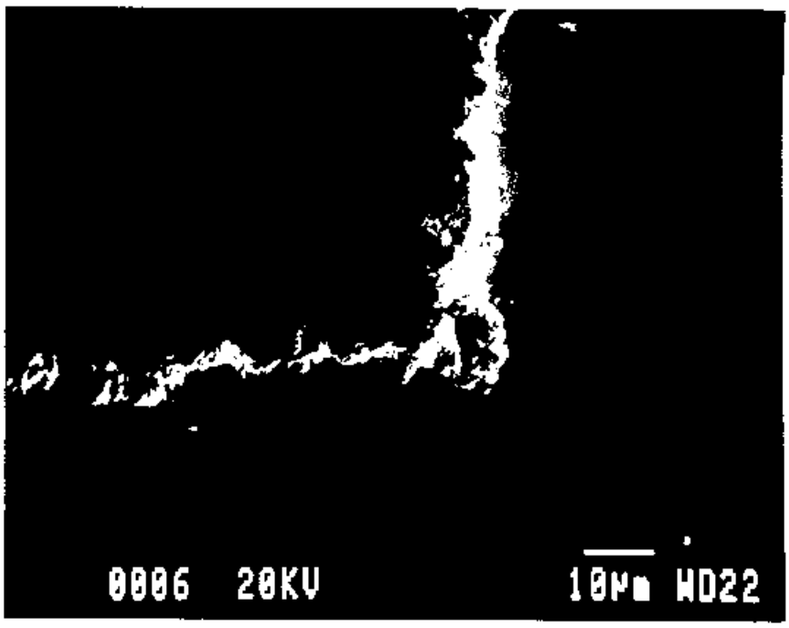


Figure 7: SEM photomicrograph at higher magnification of center left slot shown in Figure 5. 1000x

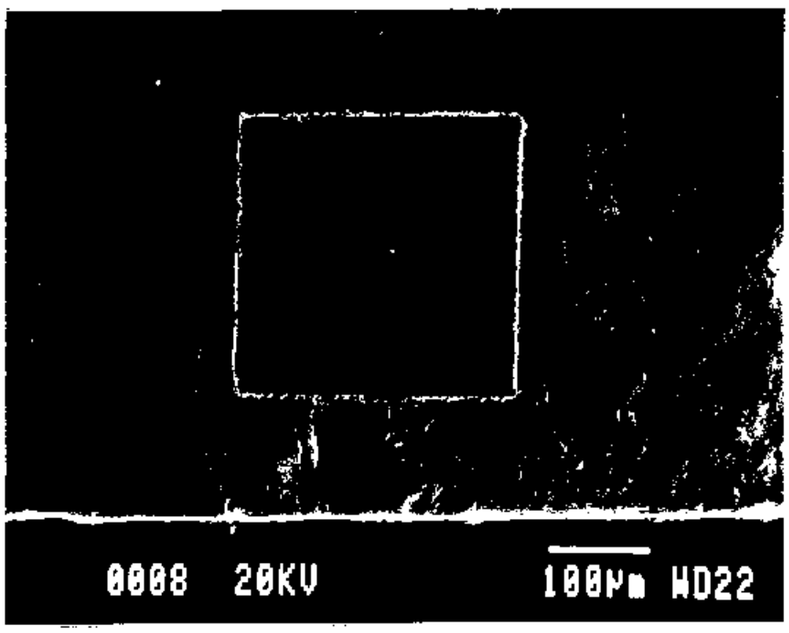


Figure 8: SEM photomicrograph of a hole laser machined through 25µm thick platinum foil using the perimeter technique. This hole was located at the edge of the piece of foil and serves to demonstrate the flatness of the foil when secured in the frame. 150x

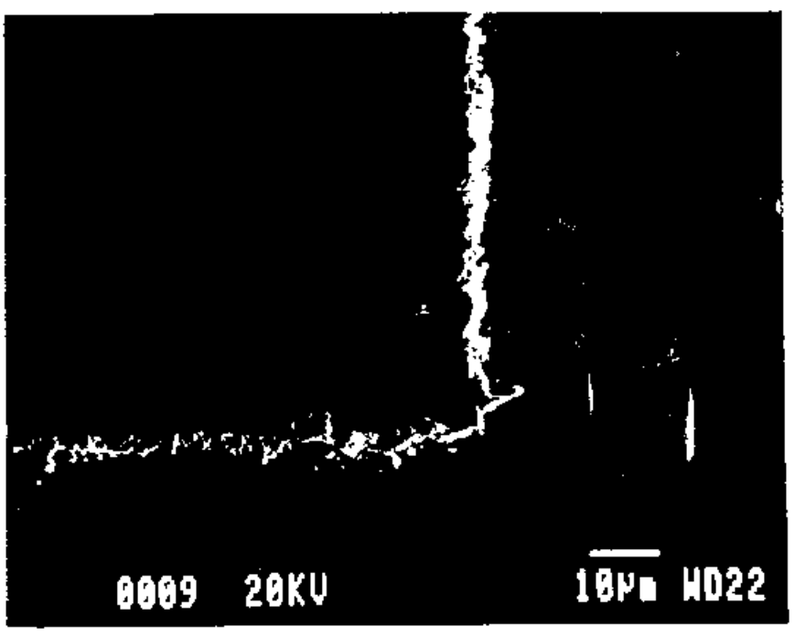


Figure 9: SEM photomicrograph at higher magnification of lower right corner of hole in Figure 8. 1000x

Foil Flexibility

Samples of foil in both 25 and 50 µm thicknesses are being investigated. Fundamental to the design of the PMP electrode is the substrate's flexibility. The thickness of the foil has a significant impact on the foil's flexibility, but we expect that the laser machined slots created along the length of the foil will also have a significant impact on flexibility, particularly once those slots are filled with elastomer. The degree of improved flexibility with machining is unknown at this point. Thick foil presents an advantage of providing more material in the case of metal loss over time. However, this must be balanced with the flexibility of the substrate. We will continue to investigate both 25 and 50 µm thicknesses with the intent of maximizing flexibility and foil thickness. These investigations will begin by having a single electrode contact path machined in a sample piece of each thickness foil. These samples should provide us with an estimation of the degree of increased flexibility after machining. Ideally, upon examination of these sample pieces, we will be in a position to select the foil thickness to be used in future studies.

Re-Alignment

When the patterned foil is returned to us for lamination, it will have to be removed from the framing device. Re-alignment of the laminated foil is crucial to the successful placement of the second pass of laser cuts, as it is these cuts that isolate each electrode contact. To aid in realignment of the laminated foil, re-alignment markers will be machined through the foil in areas outside the pattern region during the first pass of the laser. These re-alignment markers will be at the discretion of the laser personnel of PI Medical, as they will be responsible for the re-alignment. Efforts will be made to prevent these markers from being covered with the silicone elastomer lamination so that they can be visualized prior to the second pass of laser machining.

Silicone Rubber

Silicone rubber will be used to laminate the patterned foil, filling the voids created during the first laser cuts and acting to hold the patterned foil together after the second pass of laser cuts. During this second pass, the silicone rubber overlying the platinum foil will be exposed to and machined by the laser. The laser that PI Medical will be using, a Quad 4-YAG laser, is generally damaging to most formulations of silicone rubber. PI Medical has designed a laser ablatable formulation of silicone rubber, Silablate®, that is purported to be resistant to the damaging effects of the laser and is being investigated for use in the PMP electrode.

While Silablate offers the advantage of being safely laser machined, we are concerned that the formulations do not possess the required tensile strength and elongation properties that are required for use in cuff electrodes. The material has a reported tensile strength of 700 psi and a maximum elongation of 200%. Dow Corning and NuSil Silicone Technology elastomers that have been used in the manufacture of cuff electrodes typically have reported tensile strengths of 1000-1500 psi and elongations of 500-750%. Mechanical testing of the Silablate® material in our labs is ongoing. Results will be compared to the mechanical properties of the Dow Corning and Nusil Silicone Technology elastomers used in cuff manufacture.

Lamination and Second Pass of Laser Cuts

The lamination process will be performed in our laboratories and will ideally result in silicone rubber filling each void and creating a consistent thickness layer on both sides of the foil. We will work with the chosen elastomer to develop a method of creating an even sandwich around the foil. A consistent thickness of silicone rubber is needed so that the laser adequately cuts through the laminate. Our first approach will be to lay the foil directly against a layer of pre-formed Silablate® sheeting, apply uncured Silablate® elastomer against the back of the foil, and then apply a second layer of pre-formed sheeting. This assembly will be placed between plates in a press and cured. Microscopic examinations will be performed to evaluate the consistency in thickness of the laminate as well as the elastomeric filling of the pattern voids.

Laminated samples will also be returned to PI Medical for the second pass of laser machining. We will evaluate the completeness and cleanliness of these second laser cuts and

discuss with PI Medical whether the lamination process needs to be revised for improved laser machining. Additionally, we will evaluate PI Medical's success at adequately re-aligning the laminated foil by checking the accuracy in placement of the second pass of laser cuts.

Alternative Approaches

Our efforts to date have been focused on working with PI Medical. However, we will begin to investigate alternative sources for the laser machining and the possibilities of using alternative silicone rubber formulations. We will identify additional machinists with Quad 4-YAG lasers that may be able to machine the electrode pattern. We will also work to investigate alternative laser types that may not be damaging to silicone rubber. If we are successful in this approach, we can then safely use those silicone rubber formulations with previous demonstrated performance in spiral cuff electrodes.

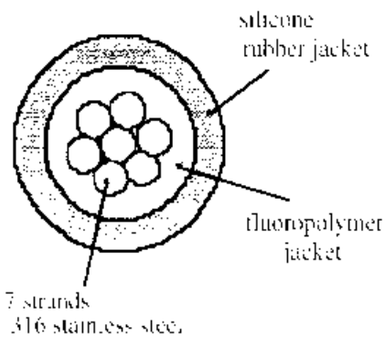
B.2.2: Lead Designs

Considerable effort has been invested in studying the lead wire for our intramuscular electrodes. Because of this wire's performance history, it has to date been adopted for use in our cuff electrodes. The wire consists of multiple strands of stainless steel insulated with a fluoropolymer coating. Fluoropolymers have been used extensively in implant devices, but generally do not bond well with other materials. For our intramuscular electrodes, this does not present a significant problem. However, in the manufacture of both spiral cuff electrodes and connectors, this non bonding of the insulated wire is a drawback.

The spiral cuff electrodes and connectors that we will investigate during this contract are made from silicone rubber and in both cases, consist of lengths of lead wire within the body of and extending beyond the silicone rubber cuff/connector. Any water or electrolyte seepage at these interfaces could promote corrosion or other modes of failure (delamination of sheeting) in the implanted electrode assembly. The poor bondability of the fluoropolymer insulation presents an increased risk of seepage at the interface and is a point of significant concern regarding the long-term reliability of these components.

In order to reduce the risks of seepage at the interface, we are investigating the feasibility of applying a thin coating of silicone rubber over the fluoropolymer insulated lead wire. The top layer of silicone rubber is expected to provide better bonding to the layers of silicone rubber sheeting and elastomer in the spiral cuff and the implantable connectors molded from silicone rubber. This second insulating layer will also provide further protection of the conducting wires. We have observed that minor, local flaws in the fluoropolymer coating can go undetected by observation but can lead to significant corrosion of the underlying wire strands.

Originally, we intended to pursue having a thin, 25µm thick coating of silicone rubber insulation applied over a multi-stranded wire that is smaller than our standard size wire. This would be performed on continuous lengths of wire through a co extrusion technique, and would result in a product with a cross sectional profile like that depicted in the figure below.



A processor, PI Medical of Portland, Oregon, was identified and consulted for this project. Two multi-stranded wire configurations were initially shipped to PI Medical for the silicone rubber co-extrusion. These wires both consisted of 7 strands of stainless steel with a fluoropolymer jacket. The first of these was our standard size wire: 7 strands of 35µm diameter stainless steel with a 75µm jacket of fluoropolymer for a final outer diameter of 255µm. The second wire configuration is a smaller size wire: 7 strands of 20µm diameter stainless steel with a 25µm jacket of fluoropolymer for a final outer diameter of 110µm. These wires were to be coated with the PI Medical silicone rubber Silablate® MED-70 to the minimal thickness possible, expected to be 25-50µm. PI Medical was able to coat both of the wire configurations with the silicone rubber jacketing, but could only go down to a thickness of 50µm. Upon receipt of this wire, our initial evaluation involved winding the wire on a mandrel in the manner of creating a helical lead cable.

We noted that the silicone rubber jacket appeared to be flaking off as the wire was wound on the mandrel. Microscopic evaluation of the coiled wire indicated that discrete sections of the silicone rubber jacket had indeed broken under the stress of winding and pulled away from the underlying fluoropolymer coating. The silicone rubber elastomer, Silablate® MED-70, has limited elongation and tensile strength, and was not appropriate for the tensile and compressive loads that are placed on the coiled wire lead cables.

We again consulted PI Medical and because of the limited physical properties of their elastomers, they decided to use another silicone rubber product for the co extrusion. A liquid silicone rubber formulation from NuSil Silicone Technologies, MED 4950, was chosen for its ultra high tear strength, elongation, and tensile properties. Fifty feet of a slightly different wire configuration was sent to PI Medical for the co-extrusion. This wire consisted of 7 strands of 35µm diameter stainless steel, but with only a 50µm jacket of fluoropolymer, for a final outer diameter of 205µm. PI Medical was able to process this wire and apply a 50µm coating of silicone rubber.

This small sample of wire has recently been received, and evaluation has begun. Because of the problems with the first coating attempt, our initial objective was to wind the wire and determine if the silicone rubber jacket suffered immediate failure. Lengths of wire were wound on a mandrel and through visual and low power microscopic evaluation, the silicone rubber was not observed to be fracturing during the winding process. However, it was noted that the silicone rubber jacket, like the silicone rubber sheeting we have previously investigated, is 'sticky'. The wire adhered to itself and to the mandrel upon winding, requiring significant effort to remove the mandrel and leading to a distorted and damaged lead cable. Surfactant coating (Liquinox® cleaner) applied to the wire and the mandrel helped to reduce this stickiness, but was not entirely effective. Scanning electron microscopy evaluation of this wire, including samples that have been wound, has begun. In vitro testing and further analysis of the silicone rubber coated wire will likely begin soon, although these evaluations will be limited by the relatively small length of wire available.

In addition to our efforts working with PI Medical, we have begun investigating alternative sources and approaches for the silicone rubber coating of our lead wires. Specialty Silicone Fabricators, the company that processes our new silicone rubber sheeting, was contacted regarding this project. Specialty Silicone Fabricators has had prior experience applying layers of silicone rubber over fluoropolymer and provided some advice on how to best approach this project. First, they recommend that a surface treatment be applied to the fluoropolymer in order to improve the bondability of the fluoropolymer with the silicone rubber. The two materials will not chemically bond, but a roughened fluoropolymer surface will improve the mechanical bonding between the two materials. The roughening of the fluoropolymer can be done through a chemical etchant solution, like Tetra Etch, or can be done through a corona etch, where the material is exposed to a high frequency voltage. We have identified a source for continuous length corona etching of our wire, as the chemical etchants are more amenable to batch processing and require and generate toxic substances. To apply the silicone rubber, Specialty Silicone Fabricators states that either a dip coating or a co extrusion process be employed. The dip coating process could likely result in a thinner overall jacket of silicone rubber, on the order of 25µm. However, dip coating is a batch process and would not be appropriate for continuous lengths of wire. Using a co-extrusion technique, the minimal applied thickness of silicone rubber would likely be 50µm, but the process could be performed on continuous lengths of wire. Quotes for the corona etching and for the co extrusion of the silicone rubber have been requested, and in the following weeks we will likely pursue this alternative course. We can then compare wire samples from these two sources and determine which, if either, warrant continued investigation.

SECTION C. IN VIVO EVALUATION OF ELECTRODES

C.1: Electrode Selectivity

Our primary objective in our planned in vivo studies is to demonstrate selective activation between adjacent fascicles within a nerve trunk, between the two muscles served by a single fascicle of a nerve trunk, and between two muscles of many that are served by a single fascicle of a nerve trunk. The focus of our efforts during this reporting period has been on modifying the transduction apparatus to provide more stable measurements and to improve the software used for data collection.

Transducer Calibration

The JR3 moment sensor was sent out to be upgraded and recalibrated.

Hardware Modifications

Evaluation of nerve cuff stimulation is based on torque measurements made at the ankle joint that are calculated from the forces and moments recorded by the transducer. These forces and moments are transferred to the transducer by a shoe pad attached to the animal's foot and to the JR3 transducer. To minimize errors in the transfer of these forces, the connections between the shoe pad and the transducer and between the shoe pad and the animal's limb must be completely rigid. Any slip between the limb, the foot pad, and the transducer will lead to inaccurate measurements. Additionally, correct placement of the animal's limb is crucial to the appropriate calculation of ankle torques. Ankle torque is calculated based on measured force and distance between the transducer and the center of rotation of the ankle. Both of these issues, system rigidity and ankle alignment, were addressed through modifications to the system hardware.

The previous shoe pad had been secured to a shaft that was attached to the JR3 transducer. The shoe pad is now mounted flat against the transducer and is secured with four machine screws. The shoe pad serves as the interface between the animal's lower leg and the measurement apparatus and any motion between the two should be minimized. Multiple cable ties have been used to secure the animal's paw. These cable ties are now used in combination with a thermoplastic tongue incorporated within the shoe pad that distributes the forces from the cable ties and acts to further secure the foot.

Correct placement of the animal's limb in the stereotaxic frame, particularly the placement of the ankle joint, is essential to obtaining meaningful results. In previous studies, placement of the ankle joint was based on a visual assessment, which proved to be both time consuming and susceptible to errors. In this visual assessment, the ankle joint was viewed from multiple angles to determine whether it was properly centered under the axis of rotation of the frame (Figure 10a). To aid in identifying the center of rotation and placing the ankle joint at that point, a modification to the frame was implemented. A hole was drilled through the main joint of the ankle rotation point of the stereotaxic frame, and through this hole a rod is inserted. This rod is used as a guide to position the ankle at the center of rotation of the transduction apparatus (Figure 10b).

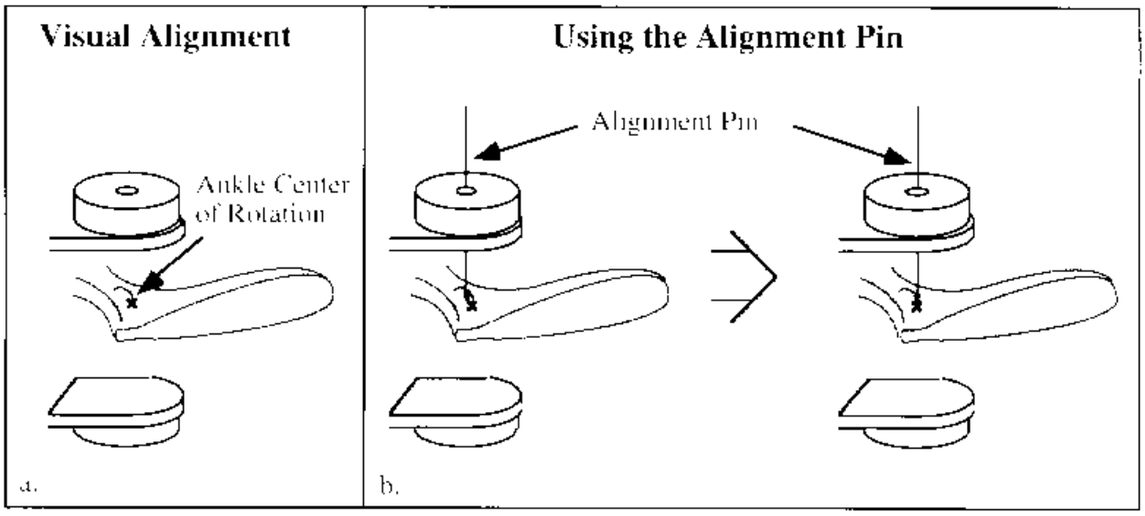


Figure 10: Comparison between the alignment of the ankle's center of rotation using visual inspection only (frame a) and using the new alignment pin (frame b). The 'x' in each frame indicates the center point.

Both hardware modifications, the improved foot pad and the ankle joint alignment pin, are presented in the following figure.

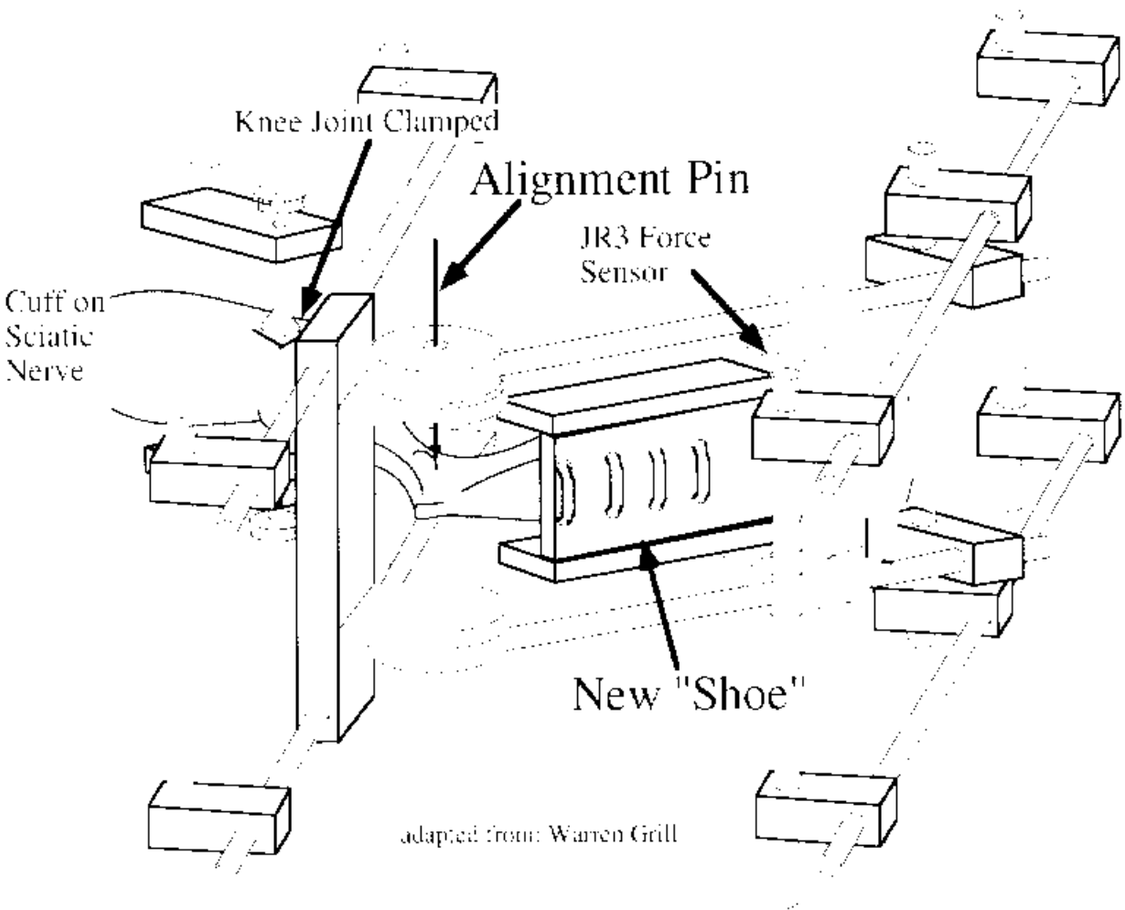


Figure 11: Schematic of the stereotaxic frame used for torque measurement. Note changes to the shoe where the paw is firmly fastened. An alignment pin was also added to the rotational point so more accurate alignment of the ankle joint can be performed.

Software Modifications

Cuff electrodes can produce a high degree of selectivity when stimulated using conventional pulse paradigms. A further increase in selectivity may result with the use of new techniques, which include field steering and pre pulse modification of excitability. We plan to evaluate these techniques in our animal studies. We have modified our stimulator software to be able to use the waveforms shown in Figure 12.

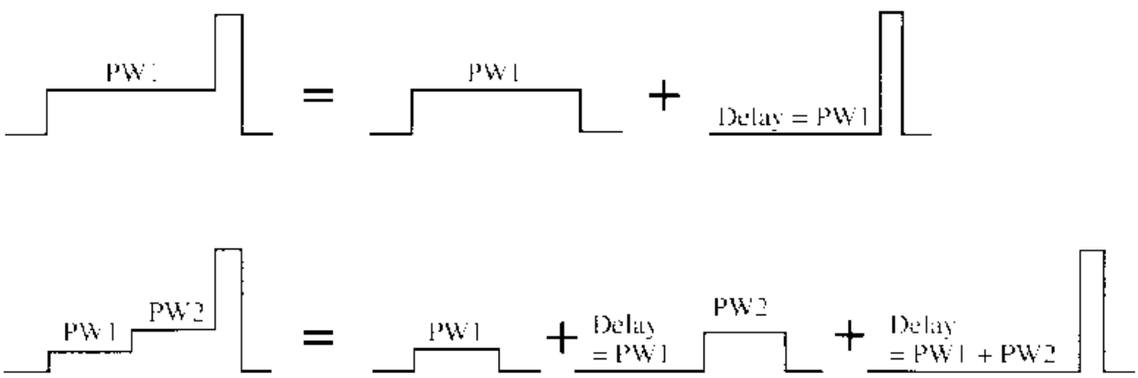


Figure 12: Pre pulse waveforms and methods used to generate them.

We plan to begin animal experiments in the next reporting period.

SECTION E. PREPARATION FOR HUMAN FEASIBILITY TESTING

Upper Extremity

In meetings with our upper extremity collaborators, we are exploring cuff electrodes as a part of their hand grasp system, with the idea that cuff electrodes would directly replace some or all of their muscle-based electrodes. Our approach is intended to be three-tiered: the first step would involve per-operative trials of cuff electrodes in patients not necessarily limited to those candidates for a hand grasp neuroprosthesis; the second step would involve short-term chronic (<3 months) percutaneous implants in patients scheduled for a hand grasp neuroprosthesis; and the third phase would involve long term implantation of cuff electrodes as part of a hand grasp system. This approach now appears to be limited by problems we had not previously considered. Our collaborators have advised us that the short-term studies would be fairly limited both in duration and in numbers of patients involved because of the risks of using a percutaneous system. They have stressed that to be clinically feasible and to be attractive to patients, any long-term application must be fully implantable, which means that a suitable implantable stimulator should be available.

A major unresolved impediment to the development of a fully implantable cuff-based system is the identification or development of an appropriate stimulator. The stimulator currently used in the hand grasp neuroprosthesis is inappropriate for use with a cuff electrode. Specific issues of incompatibility include: stimulus range and resolution; pulse control mode; anode and cathode control; stimulus pulse shape; and frequency. Their present stimulator produces currents in the range of 4-20 mA, with a resolution of several mA. Cuff electrodes would require a current range from 0 to 5 mA, with a resolution of 25 μA. Their stimulator relies on pulse width modulation, whereas cuff electrodes are ideally controlled by pulse amplitude modulation. A common, distant anode is used in their system. If steering is to be used with cuff electrodes, switchable anode and cathode channels are needed. New stimulus paradigms, including blocking and pre-pulse techniques, require unique stimulus waveforms that the collaborator's stimulator cannot produce. Experience suggests that the development of a stimulator to be used for multi-contact cuff applications will require a significant effort in design and fabrication, particularly if it is to be ready three years hence.

In the current cost conscious medical community, per-operative testing has become much more difficult. Patients undergoing carpal tunnel release surgery, a large potential population, would likely be placed at too high a risk of surgical trauma to their nerves to justify per-operative placement of a cuff electrode. Further, in these patients, the operation would be extended from 10 minutes to over an hour, as the necessary exposure site for cuff implant would involve additional surgical time. Any additional costs resulting from this increased surgical time would be accrued to the hospital and/or researcher. Patients with neuromas or amputations would be at low risk of surgical trauma, however, evaluation of the motor function derived through the cuff electrode would be severely limited. We will continue to explore opportunities to evaluate the cuff electrode system in a per-operative environment.

Our collaborators have provided suggestions for applications outside of the upper extremity hand grasp application where the risks and costs of a per-operative trial are better balanced. The first of these would be in patients undergoing ulnar nerve exploration at the elbow. This operation is fairly common, although the nerve is usually somewhat diseased at the exposure site. The extent of disease is unlikely to be so severe that visual assessment of motor function derived through the cuff electrode could not be performed. However, any quantitative assessment in these patients may be made difficult because of the high numbers of sensory fibers in the ulnar nerve at the exposed site. A second possible per operative application would be nerve mapping, both in the upper arm and in the brachial plexus region. However, opportunities for these surgical explorations are more limited.

Several new applications were explored. First is the use of cuffs on the spinal nerves or ventral roots at C5 C8. This type of system would provide stimulation to a large number of muscles in the upper extremity, conceivably through a single incision site, and could be applicable to a new patient population. The second suggestion is to use cuffs for blocking unwanted motor

activity in stroke, spinal cord injury and cerebral palsy patient populations. These cuffs would be used to block spasticity and potentially, to generate more normal motor functions.

In future meetings with our collaborators, we will further consider these clinical applications, and any others and better define what our approach to clinical implementation should be. Whatever the application, the collaborators have continuing concerns about the safety of nerve cuff electrodes. We will continue to address those concerns, present our histological observations to our collaborators, and discuss what studies may be performed within the scope of this contract to demonstrate cuff safety.

Lower Extremity

An immediate clinical application for cuff electrodes in the lower extremity is to the nerve serving the gluteus maximus muscle. In their current implant system, our collaborators place an epimysial electrode on the gluteus maximus muscle. Their current exposure site is deep, and reaches within close proximity of the gluteal nerve, meaning little additional surgical exposure would be required for cuff implant. These collaborators have done several cadaver dissections, and have noted that at the exposure site, approximately 15 mm of nerve length is available, more than sufficient room for a cuff implant. The cuff in this application would only need to be monopolar, as non-selective recruitment of the gluteal nerve is desired. From their previous experience, the collaborators have noted a significant amount of fat surrounding the gluteal nerve at the exposure site and are concerned about whether this fat must be removed prior to cuff electrode implant. Removal of the fat will require additional surgical time and of course, handling of the nerve itself. We are unsure of the significance or impact of fat surrounding the nerve, as it has not been a factor in our laboratory studies on cats.

A second candidate site for feasibility studies of cuff electrodes would be in quadriceps activation. One or 2 cuff electrodes would be placed on the femoral nerve 6-8 cm distal to its major branching point, and after the branch to rectus femoris has exited. The cuffs, again, would only need to be monopolar.

Discussion of per-operative trials in the lower extremity was limited as the orthopedic surgeon was not in attendance. However, we have been in contact with the orthopedic surgeon and his participation in our clinical collaboration is expected. In future meetings, we will discuss with the surgeon what opportunities exist for per-operative trials of cuff electrodes during routine surgical explorations of the nerves in the lower limb.

In the next months, our collaborators anticipate performing additional cadaver dissections. During these dissections, they expect to practice their exposure and implant technique, to explore the neuroanatomy at the exposure site(s), and to make measurements of nerve diameters and available lengths. Members of our laboratory will participate in these dissections and will provide to the collaborators sample cuffs to be used for mock implantation.